MARKED-UP VERSION OF THE AMENDMENTS

IN THE SPECIFICATION:

Page 18, line 7, the paragraph starting on this line has been amended as follows:

(Amended) Also, the present invention offers a compound consisting of ribonucleic acid extracted from yeast, for example a *Saccharomyces cerevisiae* or a *Candida utilis*. Preferably, the ribonucleic acid has a nitrogen content of more ~~then~~ than 14.5% by weight and a phosphorus content of more ~~then~~ than 8.5% by weight, more preferably a nitrogen content of more ~~then~~ than 14.7% by weight and a phosphorus content of more ~~then~~ than 8.6% by weight, even more preferably a nitrogen content of more ~~then~~ than 15.0% by weight and a phosphorus content of more ~~then~~ than 9.0% by weight.

IN THE CLAIMS:

Claim 7 has been canceled without prejudice or disclaimer.

Claims 1, 10-11, 20-22 and 39-45 have been amended as follows:

1. (Twice Amended) A method for the prevention or treatment of inflammation or inflammatory-related disorder selected from the group consisting of infarct, arthritis, diabetes, artherosclerosis, tumor, hepatitis, infection, and neuro-degenerate diseases, comprising administering to a mammal in need of such treatment a composition comprising total yeast ribonucleic acid and a pharmaceutically acceptable vehicle, carrier, or diluent, said composition comprising said ribonucleic acid in an amount effective to ameliorate symptoms of inflammation or inflammatory-related disorder,

wherein said composition is administered so that said ribonucleic acid is present into the mammal's blood.

10. (Amended) A method in accordance with claim 1, wherein said ribonucleic acid has a nitrogen content of more ~~then~~ than 14.5% by weight.

11. (Amended) A method in accordance with claim 1, wherein said ribonucleic acid has a phosphorus content of more ~~then~~ than 8.5% by weight.

20. (Three Times Amended) A pharmaceutical composition for the treatment or the prevention of inflammation or inflammatory-related disorder, comprising total yeast ribonucleic acid and a pharmaceutically acceptable vehicle, carrier, or diluent, wherein ~~the composition comprises at most 2.0% by weight of DNA relative to the total weight of nucleic acids in the composition~~ said ribonucleic acid has a nitrogen content of at least 14.7% by weight and a phosphorus content of at least 8.6% by weight.

21. (Amended) A pharmaceutical composition in accordance with claim 20, wherein said ribonucleic acid has a nitrogen content is more ~~then 14.5%~~ than 15.16% by weight.

22. (Amended) A pharmaceutical composition in accordance with claim 20, wherein said ribonucleic acid has a phosphorus content of more ~~then 8.5%~~ than 9.05% by weight.

39. (Amended) The method of claim 1, wherein the composition comprises ~~at most 2.0% by weight of DNA relative to the total weight of nucleic acids in the composition~~ at least about 14.7% by weight of nitrogen and at least about 8.6% by weight of phosphorus.

40. (Amended) The method of claim 1, wherein the composition comprises ~~at most 1.2% by weight of DNA relative to the total weight of nucleic acids in the composition~~ at least about 15.16%

by weight of nitrogen and at least about 8.6% by weight of phosphorus.

41. (Amended) The method of claim 1, wherein the composition comprises ~~at most 1.1% by weight of DNA relative to the total weight of nucleic acids in the composition~~ at least about 15.49% by weight of nitrogen and at least about 9.05% by weight of phosphorus.

42. (Amended) The method of claim 1, wherein the composition comprises ~~at most 1.0% by weight of DNA relative to the total weight of nucleic acids in the composition~~ more than 15.0% by weight of nitrogen and at more than 9.0% by weight of phosphorus.

43. (Amended) The composition of claim 20, comprising ~~at most 1.2% by weight of DNA relative to the total weight of nucleic acids in the composition~~ at least about 15.16% by weight of nitrogen and at least about 8.6% by weight of phosphorus.

44. (Amended) The composition of claim 20, comprising ~~at most 1.1% by weight of DNA relative to the total weight of nucleic acids in the composition~~ at least about 15.49% by weight of nitrogen and at least about 9.05% by weight of phosphorus.

45. (Amended) The composition of claim 20, comprising ~~at most 1.0% by weight of DNA relative to the total weight of nucleic acids in the composition~~ more than 15.0% by weight of nitrogen and more than 9.0% by weight of phosphorus.

New claims 46-55 have been added.

REMARKS

By the present amendment, claims 1, 10-11, 20-22 and 39-45 have been amended and new claims 46-55 have been added. The specification has been amended to correct a misspelling.

Support for the amendments is found in the original application, in particular on page 43, last paragraph (infarct), page 52, second paragraph (arthritis), page 54, second paragraph (diabetes, artherosclerosis, tumor, hepatitis, infection, neuro-degenerate diseases), in original claims 10-11 and 21-22 (N ≥14.5%, P ≥ 8.5%), on page 18, third paragraph (N ≥14.7%, P ≥ 8.6%, N ≥ 15.0%, P≥ 9.0%) and on page 27, lines 4-5, i.e., second and third rows of Table 1 (other N, P values).

Claims 1-6 and 8-55 are pending in the present application. Claims 1-6, 8-19, 23-37 and 39-42 and 46-55 are directed to methods for the treatment of various affections comprising administration of total yeast RNA, and claims 20-22, 38 and 43-45 are directed to a composition comprising total yeast RNA.

In the Office Action, claims 7, 10-11 and 21-22 are objected to. It is pointed out that the term "than" is misspelled in claims 11, 12, 21 and 22, and it is alleged that claim 7 is substantially a duplicate of claim 1.

Claims 11-12 and 21-22 have been amended to correct the misspelling and claim 7 has been canceled. Accordingly, it is submitted that the objections should be withdrawn.

Next, in the Office Action, claims 20-22 and 38-45 are rejected under 35 U.S.C. 112, first paragraph, for lack of written description. It is alleged in the Office Action that the ranges "at

most ...% by weight of DNA relative to the total weight of nucleic acids in the composition," as recited in claims 20-22 and 39-45, are not supported by the original application.

Reconsideration and withdrawal of the rejection is respectfully requested. It is submitted that the DNA content can be inversely correlated to nitrogen and phosphorus content as explained and illustrated in the present application, in particular on page 18, third paragraph and in Example 1.1 on pages 26-27. Accordingly, ranges defining a maximum content of DNA correspond to ranges defining a minimum content of nitrogen and/or phosphorus. However, for clarity, nitrogen and phosphorus contents have been explicitly recited in the claims. Literal support is found for the recitations in the original application, in particular in original claims 10-11 and 21-22 as well as on page 27, lines 4-5 and 8.

In view of the above, it is submitted that the lack of written description should be withdrawn.

Next, in the Office Action, claims 1, 6-19, 23-24, 33 and 39-42 are rejected under 35 U.S.C. 103(a) as obvious over US 5,712,256 to Kulkarni et al. (**Kulkarni**) in view of US 3,615,654 to Ayukawa et al. (**Ayukawa**). It is alleged in the Office Action that Kulkarni teaches administering yeast RNA to promote or enhance wound healing, and that Kulkarni observes that a wound includes a phase of acute inflammatory response. It is also alleged that it would have been well known to prepare yeast RNA with a reduced DNA content, as purification would have been desirable.

Reconsideration and withdrawal of the rejection is respectfully requested.

With respect to claim 1 and the claims dependent thereon, it is submitted that Kulkarni recommends yeast RNA as a treating agent for wound healing. Specifically, Kulkarni is limited to "wound healing in response to trauma or insult, which is the goal of the present invention [of Kulkarni]" (col. 6, lines 12-14), in which "insults" is defined as including "trauma, injury, either external or internal that would require immediate repair in order to maintain proper body physiology and function" (col. 7, line 67 to col. 8, line 2). In particular, Kulkarni distinguishes its invention from prior publications disclosing the use of yeast RNA to address affections that are "continual and physiological distinct from wound healing" such as intestinal repair (col. 6, lines 7-14) or other "non-trauma or insult problems" such as malnutrition (col. 6, lines 39-40).

Further, Ayukawa fails to remedy the deficiencies of Kulkarni, because Ayukawa does not provide any particular suggestion for using its yeast RNA by-product apart from the food industry. Specifically, Ayukawa discloses that "ribonucleic acid is useful in a wide variety of end-uses, such as in the food industry, particularly if it is of relatively high purity" (Ayukawa at col. 1, lines 29-30).

In contrast, in the presently claimed method as claimed in claim 1 and the claims dependent thereon, total yeast RNA is administered to prevent or treat disorders that are generally not wound-related, specifically, infarct, arthritis, diabetes, artherosclerosis, tumor, hepatitis, infection, and/or neuro-degenerate diseases, as recited in present claim 1. The results obtained with the presently claimed method to address such disorders are completely unexpected, based on the fact that Kulkarni, which focuses on wound-related disorders exclusively, as discussed above,

provides only a general conjecture that "nucleotide supplemented diets improve rapidly the host immune system" (col. 7, lines 53-55) and fails to teach or suggest addressing disorders other than wounds. These results are also completely unexpected based on Ayukawa which does not discuss uses of ribonucleic acids apart from the food industry. Therefore, present claim 1 and the claims dependent thereon are not obvious over any combination of Kulkarni and Ayukawa.

In addition, with respect to claims 11 and 39-42, and 55, it is submitted that Ayukawa and Kulkarni fail to teach or suggest the phosphorus and nitrogen contents recited in these claims.

Specifically, Ayukawa discloses only a "pure ribonucleic acid having 8.5% phosphorus and 15.1% nitrogen (col. 7, lines 24-25). Since Ayukawa teaches that "relatively high purity" is advantageous for the food industry (col. 1, lines 29-30), and that its compound having 8.5% phosphorus and 15.1% nitrogen is "pure" (col. 7, lines 24-25), Ayukawa does not provide any particular motivation to further purify a ribonucleic acid-containing composition for any purpose, let alone for pharmaceutical use.

Further, Kulkarni teaches that "wound healing can be greatly enhanced by the inclusion of nucleotides and/or substances that include essential nucleotides, such as RNA, DNA, oligonucleotides, purine and pyimidine bases, or any other source in a pharmaceutical preparation" (col. 7, lines 36-39), and that "In some preferred embodiments of this invention, the nucleotide component comprises RNA, adenine, uridine, inosine or a mixture thereof" (col. 8, lines 12-14). In other words, Kulkarni is not concerned about the purity of ribonucleic acid but about the total nucleotide content, whether these nucleotides are provided by ribonucleic acids, desoxyribonucleic

acids, or otherwise. Thus, Kulkarni does not provide a particular motivation for increasing the nitrogen and/or phosphorus content of its composition. Rather, Kulkarni suggests that nucleotides from other sources than ribonucleic acids are beneficial.

In summary, neither Ayukawa nor Kulkarni suggest that improving phosphorus and nitrogen levels (i.e., purifying the ribonucleic acids) would improve the pharmaceutical activity of a nucleotide-containing composition.

In contrast, the present inventor has applied purification of yeast RNA and found that purification of yeast RNA results in considerable improvement of its activity against a specific range of inflammatory and inflammatory-related disorders, as disclosed and claimed in the present application, and as discussed and illustrated in details in the response to the previous Office Action. In particular, an advantage of increased nitrogen and/or phosphorus content is that the effect of the total yeast RNA composition can be improved. For example, Table 4 on page 31 of the present application shows that RNA-P (15.49% nitrogen and 9.05% phosphorus) results in inhibition of aggregation of thrombocytes by 84.09%, whereas RNA-PN (14.65% nitrogen and 8.54 phosphorus) results in an inhibition level of only 45.96% (the nitrogen and phosphorus contents are given in Table 1 on page 27). In other words, the stabilizing influence of total yeast RNA on erythrocyte membrane is considerably improved by reducing nitrogen and/or phosphorus content as recited in present claims 11, 39-42, and 55.

In summary, the results obtained by the present inventor are completely unexpected because Akayama is silent as to uses other than the food industry and Kulkarni suggests that

nucleotides of any origin are effective. Therefore, for this reason alone, present claims 11, 39-42, and 55 are not obvious over any combination of Kulkarni and Akayama.

In view of the above, it is submitted that the rejection should be withdrawn.

Next, in the Office Action, claims 20-22, 38 and 43-45 are rejected under 35 U.S.C. 103(a) as obvious over Iyer et al., Proc. Natl. Acad. Sci. USA, 93:5208-5212 (1996) **(Iyer)** in view of **Ayukawa**. It is alleged in the Office Action that it would have been obvious to reduce the DNA content of the yeast RNA preparation of Iyer as it would have been desirable to purify the yeast RNA, for example to practice the oligonucleotide probe labeling in Iyer or Northern blot analysis.

The rejection is respectfully traversed. Applicant urges that Iyer itself does not teach or suggest purifying the yeast RNA. Further, the existence, even if well known, of purification methods, such as disclosed in Ayukawa, fails to provide the specific teaching or suggestion which is legally required to establish obviousness in the absence of a specific incitation to use purification in Iyer. See MPEP 2143.01 (the prior art must suggest the desirability of the claimed invention; the fact that a claimed invention is within the capabilities of a person of the art, or that references can be combined or modified, are not sufficient to establish prima facie obviousness).

Specifically, here, Ayukawa discloses a yeast RNA-containing product but only states generally that "ribonucleic acid is useful in a wide variety of end-uses, such as in the food industry, particularly if it is of relatively high purity" (col. 1, lines 28-30). Thus, in the absence of any teaching or suggestion in Iyer or Ayukawa about any advantages of purifying yeast RNA,

a person of ordinary skill in the art would have no particular motivation to practice the probe labeling of Iyer or any other experiment after purifying the composition to reduce DNA content.

In contrast, the present inventor has applied purification of yeast RNA in a totally different area than Iyer and Ayukawa, i.e., the medical field, and found that purification of yeast RNA results in considerable improvement of its activity against a specific range of disorders, as disclosed and claimed in the present application, and as discussed above. These results are completely unexpected based on Iyer whose only goal is to perform nuclease analysis, particularly in view of the fact that Iyer is satisfied with using unpurified RNA and does not teach or suggest any purification step. These results are also completely unexpected based on Ayukawa because Ayukawa focuses on reducing nucleic acid content in cells (see in particular the abstract, last sentence) and not in utilizing extracted nucleic acids, as discussed above. In short, these results are completely unexpected because neither Iyer nor Ayukawa suggests or expects any advantage of purifying yeast RNA to improve phosphorus and nitrogen contents. Therefore, present claims 20-22, 38 and 43-45 are not obvious over any combination of Iyer and Ayukawa.

In view of the above, it is submitted that the rejection should be withdrawn.

In conclusion, the invention as presently claimed is patentable. It is believed that the claims are in allowable condition and a notice to that effect is earnestly requested.

In the event there is, in the Examiner's opinion, any outstanding issue and such issue may be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants hereby petition for an appropriate extension of the response period. Please charge the fee for such extension and any other fees which may be required to our Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, WESTERMAN & HATTORI, LLP

By: Nicolas Seckel

Nicolas E. Seckel
Attorney for Applicants
Reg. No. 44,373

Atty. Docket No. 000152
Suite 1000
1725 K Street, N.W.
Washington, D.C. 20006
Tel: (202) 659-2930
Fax: (202) 887-0357
NES:rep